Crisp et al. Applicant therefore has amended claims 1 and 15, to more particularly define over the alleged prior art of record.

In view of the above amendments, Applicant respectfully submits that the amended claims in the Application are clearly allowable over the prior art Duclos et al in view of Crisp et al.

Referring now to Duclos, United States Patent No. 5,776,495, the disclosure includes an extensive list of actives which are difficult, if not impossible to dissolve in water. The list is extensive including over 70 actives identified in the list. Respectfully, it is submitted that there is no way that Duclos intended or at least perfected an understanding of how the various actives might be incorporated in a co-precipitate formulation. Frequently, within the pharmaceutical industry what might work in a technique with one active will not work with another. No where within the Duclos reference is there any discussion of cefuroxime axetil other then a listing of cefuroxime (not the ester form thereof) in the list of actives. It appears that Duclos went to a particular reference manual and attempted to list all of the actives that were hardly soluable in water without substantiating that his invention would apply to that list of actives. This is further supported by the breadth of the claims which are limited to progesterone and estradiol. Broad claims were not therefore allowed by the United States Patent Office as there is no enabling disclosure in Duclos that would enable one skilled in the art to determine and select cefuroxime from the entire list of 70 plus actives. What would motivate one skilled in the art to focus in on cefuroxime when there is no detailed discussion in Duclos of the advantages to be achieved in providing a co-precipitate as in Applicant's case.

Referring now to Crisp, United States Patent No. 4,820,833, it is clear that the teachings of Crisp at column 2, line 15 that Crisp had surprising found that cefuroxime axetil is advantageously used in a highly pure substantially amorphous

form. This attribute in Crisp is continued through the disclosure and repeated again for example, at column 6 at line 9. It is clear therefore from the teachings of Crisp and the examples therein that it was intended by Crisp that the end result would be a highly pure substantially amorphous form of cefuroxime axetil. Applicant does not desire to provide a highly pure substantially amorphous form. In fact, by preparing a co-precipitate the opposite is true. The teachings of Crisp therefore, point clearly away from the teachings of Duclos, and it is respectfully submitted that Duclos and Crisp would not be readily combined as they are somewhat mutually exclusive as covered by the case law previously provided to the Examiner. The Examiner is therefore referred back to that case law. Utilizing Applicant's teaching as a blueprint, and finding the components in the prior art is not permitted.

Further there is no motivation to one skilled in the art in the teachings of Duclos to even review Crisp. How would one skilled in the art be motivated to pursue the teachings of Crisp if in fact, Crisp does not suggest combining the art and clearly to the contrary desires a highly pure substantially amorphous form of cefuroxime axetil. Duclos does not point directly to cefuroxime but only provides it in a general listing which is not enabling.

To the contrary, Applicant provides a disclosure and support for the following claims.

> 1. An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and a water-soluble excipient, having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition.
>
> 15. An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and sorbital, having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition.

According to Graham and John Deere, the scope and the content of the prior art has been determined and the differences between the claimed invention and the prior art have been set out. Further, a discussion of motivation not to be found in any of the prior art references consistent with Re: Surnacker reasoning has been put forward. There is nothing to suggest within Duclos to in fact select cefuroxime axetil as the active when preparing a co-precipitate. There is nothing within Crisp that would teach or motivate one skilled in the art to combine the teachings of Crisp with Duclos in that Crisp points in substantially the other direction. Please refer to *Karsten Manufacturing Corp and Cleveland Golf Company, 242 F.3d 1376; 58 U.S.P.Q.2D 1286, March 22, 2001* wherein there must be some suggestion, motivation or teaching in Duclos and/or Crisp that would have led a person of ordinary skill in the art to select the references and combine them in a way that would produce the claimed invention.

Applicant has therefore provided amendments and submissions to the contrary, and full reconsideration is therefore respectfully requested.

Applicant has now amended the claims to limit the subject matter to the delayed disintegration of the composition which have an enhanced bioavailability to that which disintegrates within the range of 10 to 30 minutes to allow for time for transport of the active toward the small intestine for dissolution and absorption. This lack in the prior art is supported by the attached literature *Antimicrobial Agents and Chemotherapy, Feb. 1997, p. 445-448,* <u>*Nonlinear Intestinal Absorption Kinetics of Cefuroxime Axetil in Rats*</u>*, Ruiz-Balaguer et al.* in support of these statements and the claim amendments.

Should the Examiner require further data as evidence in support of this point, she is respectfully requested to advise Applicant's Agent, who would be more than

happy to provide such data. It is therefore respectfully requested that the prior art be withdrawn and the claims in their amended forms be allowed.

Attached hereto as Exhibit A is a marked-up version of the changes made to the claims by the present amendment. The attached pages are entitled **"EXHIBIT A – CLAIMS WITH MARKINGS TO SHOW CHANGES".**

Also attached hereto as Exhibit B are three sheets that contain a clean set of all pending claims following entry of this amendment. These sheets are entitled **"EXHIBIT B – CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT".** All of the currently pending claims are consolidated in this list for the convenience of the Examiner.

Should the Examiner have any questions she is respectfully requested to contact Applicants' Agent, Neil H. Hughes at (905) 771-6414 at her convenience.

Respectfully submitted,

Neil H. Hughes, P.Eng.
Registration No. 33,636
Agent for the Applicant

NHH:mse
Enclosures

EXHIBIT A
CLAIMS WITH MARKINGS TO SHOW CHANGES

Please amend the following claims.

1. (Twice Amended) [A] An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and a water-soluble excipient, having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition.

15. (Twice Amended) [A] An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and sorbital, having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition.

EXHIBIT B
CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT

1. An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and a water-soluble excipient, having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition.

2. The composition of claim 1 comprising from about 40% to about 98% by weight cefuroxime axetil and from about 2% to about 60% by weight water-soluble excipient.

3. The composition of claim 1 comprising from about 75% to about 95% by weight cefuroxime axetil and from about 5% to about 25% by weight water-soluble excipient.

4. The composition of claim 1 comprising about 90% by weight cefuroxime axetil and about 10% by weight water-soluble excipient.

5. The composition of claim 1 wherein the water-soluble excipient is selected from the group consisting of povidone, hydroxy propyl cellulose, methycellulose, lactose, mannitol and sorbitol.

6. A process of production of the composition of claim 1 which comprises:

- dissolving the cefuroxime axetil and water-soluble excipient in a solvent or a mixture of solvents; and
- evaporating the solvent or solvents.

7. The process of claim 6 wherein acetone is used as solvent.

8. The process of claim 6 wherein the solvent or solvents are evaporated by spray-drying.

9. A pharmaceutical tablet comprising the composition according to claim 1.

10. The pharmaceutical tablet of claim 9 further comprising a disintegrant.

11. The pharmaceutical tablet of claim 10 wherein the disintegrant is a water-insoluble cross-linked polymer.

12. The pharmaceutical tablet of claim 10 wherein the disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate and crospovidone.

13. The pharmaceutical tablet of claim 10 further comprising a lubricant.

14. The pharmaceutical tablet of claim 13 wherein the lubricant is stearic acid or a metallic stearate.

C2 15. An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and sorbital, having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition.

16. The composition of claim 15 comprising about 90% cefuroxime axetil and about 10% sorbital.

17. A process of production of the composition of claim 15 which comprises:
- dissolving the cefuroxime axetil and sorbital in a solvent or a mixture of solvents; and
- evaporating the solvent or solvents.

18. The process of claim 16 wherein acetone is used as solvent.

19. A pharmaceutical tablet comprising the composition according to claim 15.

20. The pharmaceutical tablet of claim 19 further comprising a disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate and crospovidone.